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Acute Promyelocytic Leukemia: All-*trans* Retinoic Acid (ATRA) Along With Chemotherapy Is Superior to ATRA Alone

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This study was conducted to compare the results of treatment of acute promyelocytic leukemia (APL) with all-*trans* retinoic acid alone (ATRA) or a combination therapy of ATRA followed by chemotherapy. Forty-three patients treated between February 1992 and February 1996 were included in this study. Eighteen patients were treated with ATRA alone and 25 patients were treated with ATRA followed by chemotherapy. The cytogenetic analysis was done in 41 patients at presentation, following treatment, and at follow-up. A complete response (CR) was achieved in 13 (72%) patients on ATRA and 19 (76%) on ATRA followed by chemotherapy. Eleven of 13 patients with response to ATRA alone relapsed with median survival of eight months (range, 1 to 28). One patient died of hepatitis in CR and one patient is alive 2 years after diagnosis. In the combination therapy arm, 10 patients are in CR with a median follow-up of 22 months (range, 6 to 56 months). After achieving a CR, four patients died due to infections during chemotherapy therapy, and only 5 of 19 patients have relapsed. Major cytogenetic response was seen in 8 of the 10 patients in whom cytogenetic data was available after treatment with ATRA at the time of remission. Similarly, 13 of 15 for whom data was available showed a major cytogenetic response after treatment with ATRA plus chemotherapy. Prior to relapse, 80% of the patients had an increase in the percentage of t(15;17) cells in the marrow. Patients with a complete hematological response but no cytogenetic response relapsed within six months. Ten patients died prior to response evaluation. Two patients who received ATRA died of retinoic acid syndrome, one of pneumonia, and one of intracranial hemorrhage. Of the six patients on ATRA and chemotherapy, four died of retinoic acid syndrome (RAS), one of intracranial hemorrhage, and one of left ventricular failure. Only one patient is alive at 24 months following treatment with ATRA alone. The relapse-free survival is 42% at four years for patients treated with ATRA followed by chemotherapy. This trial is a historical comparison of ATRA alone and ATRA with subsequent combination chemotherapy. Nonetheless, the trial shows a significant improvement in the event free survival of patients receiving chemotherapy as consolidation following ATRA. Am. J. Hematol. 60:87–93, 1999.

Key words: myeloid leukemia; chemotherapy; differentiating agents; retinoic acid syndrome; disseminated intravascular coagulation; hyperleukocytosis

INTRODUCTION

Acute promyelocytic leukemia (APL) is characterized by reciprocal and balanced translocation between the long arm of chromosome 15 and 17 [1,2]. All-*trans* retinoic acid (ATRA) has selective differentiating activity on abnormal promyelocytes in vitro and in vivo [3]. Recent studies have shown that ATRA is capable of inducing an 80 to 90% complete response (CR) in newly diagnosed APL patients [4–7] and also after the first

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relapse [8]. Because ATRA initially induces cytodifferentiation rather than immediate cell lysis of leukemic cells, response to ATRA is associated with rapid improvement of hemostatic disorder which occurs in the absence of bone marrow aplasia [5,7]. However, patients who achieved remission with ATRA and were maintained on ATRA alone relapsed rapidly [4–8]. Chemotherapy with anthracycline and cytosine arabinoside (Ara-c) resulted in a high CR rate for newly diagnosed APL patients [9–14] with a 50 to 60% relapse rate. Fenaux et al. [15] reported in their study that ATRA followed by intensive chemotherapy gives a high CR rate and may prolong the remission in newly diagnosed APL patients.

The present study was done to determine the response rates and duration of response with ATRA alone or ATRA followed by intensive chemotherapy in untreated APL.

PATIENT AND METHODS

Inclusion Criteria

Between February 1992 and February 1996, 43 newly diagnosed patients with APL were prospectively studied. The patients were followed up until December 1996. The diagnosis of APL was based on the French-American-British (FAB) group morphology [16]. The patients were 60 years or under, gave informed consent, and had no contraindications to receive chemotherapy. Cytogenetic study for t(15;17) was performed in 41 patients.

Protocol

Between 1992 and 1993, 18 patients were enrolled into this study. Seventeen patients received ATRA at 45 mg/M^2 per day orally until CR followed by 90 mg/M^2 on alternate days as maintenance until relapse. One patient received ATRA for four months followed by chemotherapy. As these patients were found to relapse early, and the only patient in sustained remission was one treated with chemotherapy following treatment with ATRA, the protocol was modified to ATRA followed by chemotherapy from 1994 onward.

Twenty-five patients were enrolled from 1994 to December 1995. Twenty-four received ATRA at an oral dosage of 45 mg/M^2 per day for 90 days, followed by four cycles of consolidation chemotherapy. The chemotherapy was given as follows: Cycle 1: Daunomycin, 45 mg/M^2 per day intravenous bolus for three days and Ara-c, 200 mg/M^2 per day as 24-hr intravenous infusion for seven days; cycle 2: Daunomycin, 45 mg/M^2 per day intravenous bolus for three days and Ara-c, 100 mg/M^2 per day as 24 hr intravenous infusion; cycle 3: High-dose Ara-c, 2 gm/M^2 12 hourly as three-hr intravenous infusion for four days; and cycle 4: The same as cycle 2. One patient who also had Pott's spine at the time of her diagnosis during this period was treated with ATRA alone. Thus, 18 patients effectively received ATRA alone and 25 patients effectively received ATRA followed by chemotherapy.

Patient Management

While on ATRA, hyperleukocytosis was prevented by the addition of hydroxyurea in a dosage of 1.0 gm twice daily if the white blood cell (WBC) count was $>5 \times 10^9$/L at presentation or on day 5, $>10 \times 10^9$/L by day 10, or 20×10^9/L at any time after initiating treatment with ATRA. Patients with early evidence of ''retinoic acid syndrome'' (RAS) such as fever, weight gain, and pulmonary infiltrate on chest X-ray received intravenous dexamethasone 10 mg 12 hourly for at least three days.

The hemostatic disorder disseminated intravascular coagulation (DIC) and/or fibrinolysis was considered significant if serum fibrinogen level was <150 mg/dl, platelet count was $<30 \times 10^9$/L, and fibrinogen degradation product (FDP) was >40 μcg/ml in the absence of liver disease. Coagulopathy was treated with transfusions of fresh-frozen plasma and platelet transfusion to maintain a platelet count $>30 \times 10^9$/L until normalization of FDP and serum fibrinogen level.

Response Assessment

CR was defined as the normalization of peripheral blood picture with disappearance of blast (<5%) and promyelocytes in the bone marrow. Partial response (PR) was defined by normalization of peripheral blood picture but persistence of blasts and promyelocytes which were less than 30% in the bone marrow. No response (NR) was defined by the presence of >30% blasts in the bone marrow. Response evaluation was done after 28 days of ATRA therapy and again at 45 days of therapy in patients achieving a PR on day 28. Cytogenetic response was described as ''major'' when there was >50% decline in the number of metaphases showing t(15;17) as compared with the initial reading, and ''minor'' when it was <50%. Complete cytogenetic response was described when none of the metaphases showed t(15;17) after therapy.

Follow-Up

These patients were followed up until relapse or death. Bone marrow examination was done on day 28 and thereafter once every three months during the first year, six monthly during the second year, and at the time of relapse. During the follow-up, cytogenetic studies were done at the time of completion of ATRA and of chemotherapy and at the time of relapse of the disease whenever possible.

Statistical Analysis

Disease-free survival (DFS) was the major study end point. DFS was calculated from the date of achieving

TABLE I. Patient Characteristics at Initial Presentation*

Characteristics	ATRA	ATRA + CT
Sex		
Male:female	15:3	13:12
Age (years)		
Median	31	31
Range	7–60	7–55
Hemoglobin		
<10 gm/dl	14	20
>10 gm/dl	4	5
Total leukocyte count		
Median $\times 10^9$/L	17	23.2
Range $\times 10^9$/L	1.0–162	1.2–98
Platelet count		
Median $\times 10^9$/L	20	34
Range $\times 10^9$/L	10–160	8–250
Coagulopathy	16	24
Blast + promyelocytes		
Up to 50%	01	02
50 to 90%	06	09
>90%	11	14
Karyotype		
t(15;17)	15	19
No metaphase	3	4
Not done	—	02

*ATRA, all-*trans* retinoic acid; CT, chemotherapy.

TABLE II. Response and Status of Patients Treated With ATRA or ATRA + CT*

	ATRA	ATRA + CT
Hematological response		
Complete response	13	19
No response	1	—
Not evaluable	4	6
Cytogenetic response		
Normal	3	5
Major response	5	8
Minor response	—	1
No response	2	1
Status		
Alive in CR	1	10
Death in CR	—	4
Relapse	12	5
Follow-up (months)		
Median	8	22
Range	1–28	6–56

*ATRA, all-*trans* retinoic acid; CT, chemotherapy; CR, complete response.

remission until the last date of follow-up, relapse, or death. The CR rate and overall survival (OS) were considered as secondary end points. OS was calculated from the date of entry into the study until the date of last follow-up or death. Early death was defined as death before response evaluation. DFS and OS were analyzed with Kaplan-Meier estimation [17].

RESULTS

The clinical features at presentation of the 18 patients who received ATRA alone and the 25 patients who received ATRA and chemotherapy are shown in Table I. The median age was 31 years in both groups. Significant coagulation abnormalities were seen in 40 patients at presentation. Pretreatment cytogenetic analysis revealed t(15;17) in 15 patients in the ATRA group and 19 patients in the ATRA with chemotherapy group. In the remaining patients no metaphase was obtained for detection of the translocation.

Response

Table II shows the response to therapy. Of the 18 patients treated with ATRA alone, 13 (72%) achieved a CR, one showed no response to ATRA, and four were not evaluable for response. The median duration for coagulation parameters to return to normal was 10 days (range, 5 to 17) after starting ATRA. In the ATRA plus chemotherapy group, 18 patients achieved CR with ATRA alone. One patient who did not show a response to ATRA achieved CR after the first cycle of chemotherapy. The CR rate was 76%. In six patients, response could not be evaluated due to early death. Following treatment with ATRA alone, cytogenetic analysis was done in 10 patients. Three patients had normal cytogenetic studies, five had a major response, and no response was seen in two patients. In the ATRA with chemotherapy group, 15 patients had cytogenetic analysis after completion of chemotherapy. Five had normal cytogenetic studies after ATRA and chemotherapy, eight had a major response, one had a minor response, and one showed no cytogenetic response (Table II).

Early Deaths

The main characteristics of the patients who had an early death are summarized in Table III. Early death occurred in 10 (23%) of 43 patients. Four patients in the ATRA group died before response evaluation. Two patients died of RAS, one had intracranial bleed, and one died of bronchopneumonia and associated uncontrolled DIC. In the ATRA plus chemotherapy group, six patients died; four patients died of RAS, one due to recurrent left ventricular failure, and one due to intracranial hemorrhage.

Follow-Up

In the group treated with ATRA alone, 11 of 13 patients relapsed from a CR at a median duration of eight months (range, 1–28). Whereas one patient died of hepatitis in CR, only one patient is alive after the follow-up at 24 months. Her initial bone marrow cytogenetics was not done. However, on ATRA at the time of response evaluation she had 57% metaphasis showing t(15;7) and on follow-up 6 months later, only 25% metaphasis were

TABLE III. Characteristics of Patients With Early Death During Therapy*

Age/sex	Bleed	WBC ($\times 10^9$/L)	Significant coagulopathy	Platelets at presentation	Survival (days)	Death
ATRA alone						
28/F	+	7.4	+	20	05	ICH
35/F	+	7.0	+	20	04	RAS
56/M	−	4.7	+	310	10	RAS
34/M	−	−	+	20	18	Pneumonia
ATRA with chemotherapy						
27/M	−	8.0	+	30	24	RAS
22/F	−	6.0	−	30	13	RAS
53/M	−	8.0	+	210	27	Rec. LVF
49/F	+	7.5	+	10	14	RAS
36/M	+	1.2	+	70	27	RAS
34/F	−	55	+	70	35	ICH

*WBC, white blood cell; ATRA, all-*trans* retinoic acid; ICH, intracranial hemorrhage; RAS, retinoic acid syndrome; LVF, left ventricular failure.

positive. She continued to be in hematological and cytogenetic remission for 24 months until December 1996. The overall survival of patients in this group is shown in Figure 1. Two patients were treated with chemotherapy after relapse, but both patients succumbed to their disease within three months. The percentage of t(15;17) increased in eight of the 10 patients at follow-up prior to relapse. Both patients with no cytogenetic response relapsed from a hematological CR within six months.

Five (26%) of 19 patients who achieved CR after being treated with ATRA and chemotherapy have relapsed in the marrow. Three of these five patients showed an increase in the percent of t(15;17) at relapse. The patient with no cytogenetic response relapsed in the marrow within six months of achieving a CR. The median duration of remission in this group of patients is 22 months (range, 6–56 months). One patient died of hepatitis in CR, two due to sepsis during bone marrow aplasia, and one patient died of Gram negative septicemia in the absence of marrow aplasia. Ten patients were alive and disease free at intervals of six to 56 months after achieving a CR. The disease-free survival of patients on ATRA and chemotherapy are shown in Figure 2.

Toxicity

Twenty-one (48%) patients developed hyperleukocytosis (peripheral leucocyte count > 20.0×10^9/L). However, none of these patients showed symptoms and signs attributable to hyperleukocytosis. Fourteen patients developed RAS. Fever, dyspnoea, and bilateral pulmonary infiltrate were present in all 14 patients with RAS. The median duration of development of RAS after starting ATRA was 10 days (range, 4 to 26). Median leukocyte count at the onset of RAS was 30×10^9/L (range, 4 to 267). Hydroxyurea was beneficial in decreasing the counts in all 21 patients with hyperleukocytosis. Eight of the 14 patients showed a dramatic response to intravenous dexamethasone. Six patients continued to have progressive respiratory distress and died due to RAS.

The other side effects of ATRA, such as dryness of skin and conjunctiva, were mild and did not require treatment discontinuation. Increase in serum triglycerides was seen in one patient and headache due to raised intracranial hypertension was seen in two adults and one child. Treatment was not discontinued for any of these side effects. Myelosuppresion was the most common toxicity seen after chemotherapy. The median duration for the total count to recover after chemotherapy was 10 days (range, 7 to 20). Two patients died of neutropenic sepsis post chemotherapy as already mentioned.

DISCUSSION

In our initial experience of newly diagnosed APL patients treated with ATRA, we confirmed the efficacy of ATRA. Our results are comparable to the CR rates reported in the literature [4–8]. CR was obtained without any signs of bone marrow hypoplasia and an increase in peripheral blood count was observed with a maximum peak on day 10. The striking feature of this treatment was not only the absence of an exacerbation of DIC, but also a correction of coagulation abnormalities within the first week. This is in sharp contrast to cytotoxic chemotherapy that is also effective in initial treatment for APL [9–13] but is associated with worsening of coagulopathies.

The duration of remission in these patients treated with ATRA alone was relatively brief. Eleven patients relapsed from CR at a median of eight months (range, 1 to 28 months). This suggests that residual leukemic cells escape the drugs effect because of either inherent insensitivity to ATRA or acquired resistance. With one exception, all of our patients who received ATRA alone relapsed, which is similar to findings in other studies [4–7,18].

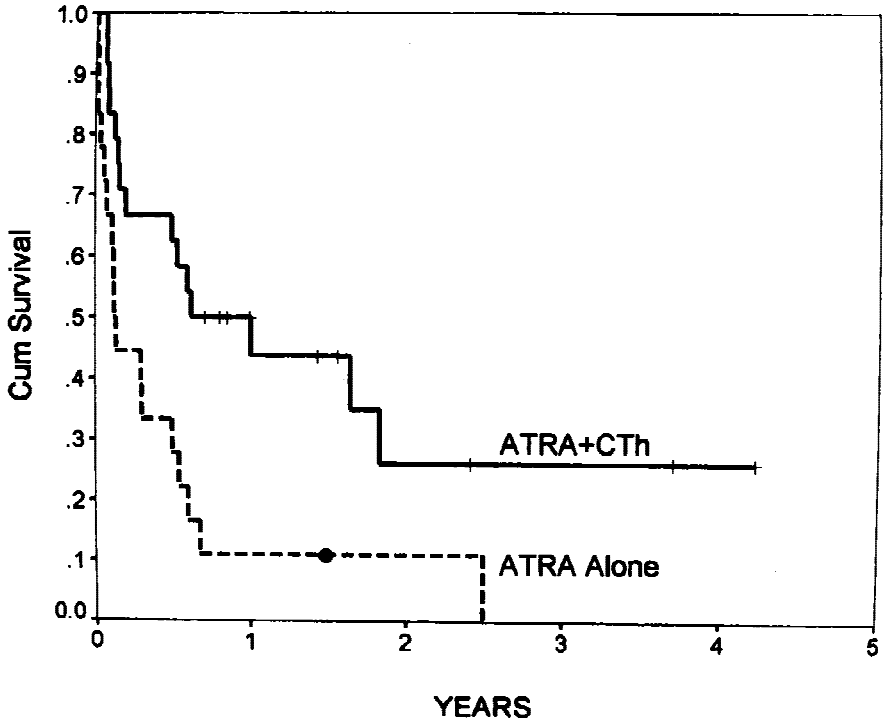

Fig. 1. Overall survival of patients treated with ATRA alone and ATRA followed by chemotherapy.

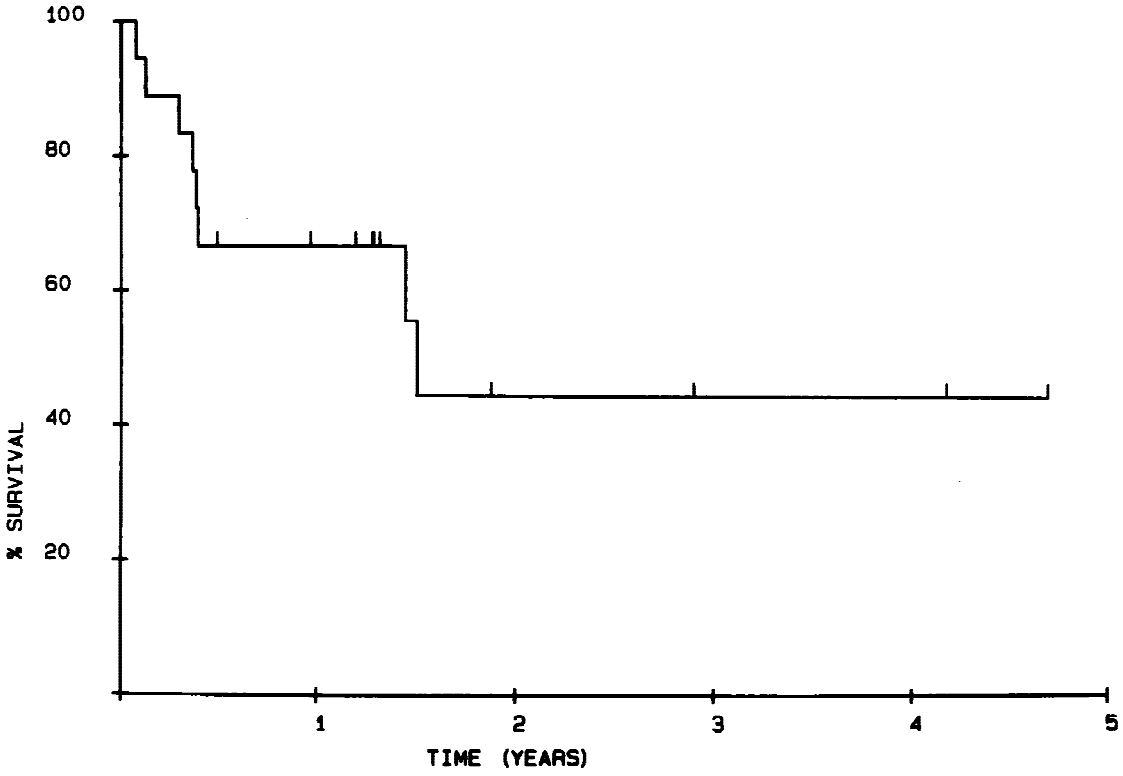

Fig. 2. Disease-free survival of patients treated with ATRA followed by chemotherapy.

The precise mechanism of ATRA-induced resistance is still unclear. The efficacy of ATRA rests on the presence of specific retinoic acid receptors and their affinity for ATRA. Alterations in these parameters may induce resistance to ATRA. Primary resistance is rarely observed if diagnosis is confirmed by t(15;17) translocation or PML-RAR-α product. Secondary resistance to ATRA is related to a feedback mechanism at reducing ATRA concentration. Enzymes implicated in the conversion of the exogenous vitamin A to retinoic acid and its metabolites are cytochrome p450 dependent and require certain cellular binding proteins such as CRABPII (cytoplasmic retinoic acid binding protein type II). ATRA therapy increases the level of CRABPII in normal hematopoietic cells. This results in an increase of proteins that induce ATRA catabolism. This may explain in part why ATRA therapy alone is unable to eradicate the leukemic clone. Other causes of secondary resistance may include mutations of retinoic acid receptor genes or selection of a non-APL clone. In subsequent patients, we consolidated the remission obtained with ATRA with intensive chemotherapy. Recently, several studies have strongly supported the superiority of combined treatment over ATRA alone [14] or chemotherapy alone [18]. Our results are consistent with the reports from other centers that compared the use of ATRA with recent or concurrent treatment with chemotherapy [15,18,19]. Although the CR rate did not alter between ATRA alone (72%) and ATRA with chemotherapy (76%) in our patients, the relapse rate in the first two years after treatment markedly decreased following therapy with ATRA and chemotherapy. Only five patients have relapsed of the 19 who achieved a CR. The median duration of remission (22 months) for this group is significantly longer than for ATRA alone (eight months). The treatment with ATRA does not eradicate molecular evidence of PML/RAR-α rearrangements from patients in complete hematological response; however, consolidation chemotherapy routinely converts these assays to negative in most patients. Serially negative tests have been associated with extended remission [20]. The relapse-free survival following ATRA and chemotherapy is 42% at four years.

An important aspect of this study is the cytogenetic analysis. Treatment with ATRA resulted in major cytogenetic response in up to 80% of patients. The patients treated with ATRA alone relapsed early despite a major cytogenetic response, whereas a significantly longer DFS was observed in patients in whom the initial response was consolidated with chemotherapy. Patients with a hematological CR but no cytogenetic response relapsed within six months of achieving CR.

A progressive increase in WBC counts is commonly seen with ATRA treatment. In our patients, hyperleukocytosis was controlled using hydroxyurea alone. This was an effective and simple method to control hyperleukocytosis. All 21 patients with hyperleukocytosis responded to hydroxyurea. Several other methods have been described in the literature to specifically control hyperleukocytosis, such as use of cytosine arabinoside and leukapharesis [18,19,21]. The use of cytotoxic therapy has been associated with severe complications of rapid cell lysis [18]. Leukapharesis is also unable to control leukocytosis effectively [21]. RAS is characterized by fever and respiratory distress, along with weight gain, lower extremity edema, pleural or pericardial effusions, hypotension, and sometimes renal failure. The spontaneous incidence of RAS was 23% in the New York experience [22,23] but was very low in the Chinese experience [4]. Fourteen patients (32%) in our series developed RAS while on ATRA. Hyperleukocytosis alone is not a predictor of whether a patient will develop RAS. Of 21 patients who developed hyperleukocytosis, only 11 progressed to RAS. This is similar to the incidence in other studies in which more than half the patients met these leukocyte criteria, yet only one fourth developed symptoms of RAS. Once RAS has developed, the addition of low-dose chemotherapy is ineffective in lowering WBC counts and leukapharesis is unable to revert symptoms. The approach used currently is to prevent RAS by administering high-dose intravenous corticosteroids (dexamethasone at 10 mg twice daily for three or more days) as soon as the first symptoms appear. This treatment has proved very efficient in preventing RAS in the New York experience and has sharply reduced the mortality from three in nine patients in their initial report, to no mortality in the last two years [18,22,23]. This approach avoids the early use of chemotherapy and its side effects. In our experience, in eight patients of 14 who developed RAS, we were able to revert the syndrome with dexamethasone; however, six patients died of progressive respiratory failure.

Resolution of coagulopathy has been reported as the earliest sign of clinical response of ATRA [24]. Of 40 patients who had evidence of coagulopathy at presentation, 18 improved by day 6 of ATRA. In three patients, DIC remained uncontrolled despite all attempts to correct it with platelets and fresh-frozen plasma, and these patients died. We have not used heparin as an anticoagulant in any of our patients.

Our data suggests that initial treatment with ATRA probably yields a very substantial antileukemic effect, perhaps exceeding that achieved by induction treatment with cytotoxic drugs. This approach to induce remission is associated with less chemotherapy-related morbidity. Hyperleukocytosis can be effectively handled with hydroxyurea alone and intensive chemotherapy can be

avoided until the patient is in complete remission. Consolidation with intensive chemotherapy is essential for prolonging the disease-free survival in these patients.

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